

Aus dem Pathologischen Institut der Universität Basel
(Vorsteher: Prof. Dr. med. A. Werthemann)

Arbeit unter Leitung von Prof. Dr. med. S. Scheidegger

**Gonadal Dysgenesis
Autopsy, Clinical and Microscopical
Findings in a Case of Turner's Syndrome**

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

RONALD C. FUERSTNER

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Recent well-documented discussions of the various forms of gonadal dysgenesis mostly present relatively young subjects discovered either by the pediatrician or the gynecologist before the age of thirty. The purpose here is to describe a case that has been verified at autopsy of a 64 year old female phenotype, originally hospitalized for a fracture of the femur. Clinical, morphological and histological aspects of this case are taken into consideration in this report.

ANAMNESIS

The patient was the second daughter of a normal couple living in Geneva. Her sister was entirely normal. Early development was uneventful according to the sister. However, the patient failed to grow properly and only reached a height of 135 cm. In school the patient had to repeat language classes after moving from a French to a German-speaking part of Switzerland but was considered otherwise to be average. She was never seriously ill and did not seek medical help either for her stunted growth or for the primary amenorrhea condition that existed. She became a seamstress and continued that occupation for the next 27 years. Past the age of 50, she became increasingly dement. She developed edema of the legs and began losing hair. At the age of 58, she was struck by an auto and suffered a fracture of the neck of the femur. This was her first hospitalization and led to the full investigation reported here. The patient never fully recovered following the accident. During the course of her prolonged confinement, she became increasingly mentally impaired. In the hospital a benign tumor of the right apical lung region was also discovered. The patient died five years after her original hospitalization. The autopsy and histological investigations were conducted at the Pathology Department of the University of Basel, Switzerland. Clinical investigations were performed by the Department of Internal Medicine of the Basel University Hospital.

PHYSICAL EXAMINATION

Upon completion of conservative therapy for the fracture, the patient was transferred to a convalescent hospital where the following findings were noted:

Appearance: small dwarf-like female with practically normal proportions.

Vital signs: Pulse 120/min. B. P. 160/100 T. 37.0 R. 24/min.

Skin: dry, scaly. Pitting edema of the lower legs, slight edema of the backs of the hands.

Hair: extremely sparse on scalp, little axillary hair, pubic hair female in distribution, scanty. The upper lip and chin are hairy. The posterior hairline is low.

Eyes: pupils equal and reactive to light. Accomodation is poor. Eye movements coordinated. Sclera white, conjunctiva pale red. No signs of daltonism.

Ears: large, low set. Auditory acuity reduced in both ears.

Nose: small, straight, congested.

Mouth and Throat: lips thin, wide mouth. Upper prosthesis, few decayed lower teeth. Pharynx clear, tonsils small.

Neck: short, freely moveable. Wide, no signs of pterygium. Thyroid non-palpable. No swellings or tenderness.

Chest and Lungs: wide, symmetrical, flat. Equal expansion. Percussion uniform. Auscultation reveals increased expiratory phase, few rhonchii. Diaphragm excursion one fingerbreadth, Th. 10-11.

Heart: regular rhythm, tachycardia, no abnormal pulsations or thrills, point of maximal impulse non-palpable. Heart sounds clear, $A_2 > P_2$.

Breasts: extremely widely spaced, small, flat nipples. No palpable breast tissue. No secretions, tenderness or palpable lymph nodes.

Abdomen: flat, no masses. Liver and spleen within normal limits.

Genitalia: the labia majora are flat, rough, non-symmetrical. The labia minora are extremely undeveloped. Bimanual inspection reveals a very narrow vagina and a practically non-palpable uterus.

Extremities: long upper limbs, fingers short and fat, fingernails small and thin, brittle. Right leg shortened slightly. Left tibia deformed. Swelling of both feet and ankles. Pulses palpable.

Nervous System: Reflexes all positive and normal, negative Babinsky, negative Romberg.

LABORATORY FINDINGS

Blood:

Sedimentation rate constantly increased, varying between 11/22 to 54/82.

Hb.	77 %
Erythrocytes	3.9 million
Leucocytes	9,200 - 11, 350
Segmented Neutrophiles	71 %
Band Neutrophiles	15 %
Lymphocytes	7 %
Eosinophiles	3 %
Basophiles	0.5 %
Monocytes	7 %
Calcium	8.2 mg %
Urea Nitrogen	26 mg %
Nonprotein Nitrogen	27 mg %
Total Serum Protein	7.2 g %
Serum Albumin	2.9 g %
Serum Globulin	4.3 g %
A/G ratio	1.5
Serum Iron	76 gamma %
Alkaline phosphatase	3.87 units
Wassermann Reaction	neg.
Creatinine clearance	93 ml/min.
Phenolsulfonphthalein test	70 %
Protein Bound Iodine	2.6 gamma %
Basal Metabolism	+ 16 % and + 34 %
Thorn Test	97 % drop of circulating Eosinophiles after 25 mg. ACTH 8 hrs. previously.

Sex Hormones:

Phenolsteroids	66 µg/24hrs.	(N = 10-45 Female) (2.5-10 Male)
Pregnandiol	4.4 mg/24 hrs.	(N = 2-13)
Gonadotropins	less than 20 Ut.	Mouse U./24 hrs. (N = 10-40 Male) (10-50 Female)

Chromosome Studies:

Drumsticks	- 0	(1500 leucocytes counted)
Sex Chromatin	- 0 %	(300 nuclei of buccal smear cells counted) Childrens Hosp. 0.0 % (buccal smear) Anatomy Institute.

X-ray Findings:

1. Severe Osteoporosis
2. Pertrochanteric femoral neck fracture
3. Hyperostosis frontalis interna
4. Small Sella turcica
5. Lungs: Shadow of the right apical region carrying into the left para-mediastinal area.

POST MORTEM S. N. 298/63

Again, the dwarf-like appearance was noticed and the following measurements taken: length 135.2 cm., weight 44.7 kg., arm span 143 cm., heel-symphysis length 63 cm. The skin was noted to have numerous pigmented naevi in the face and neck regions as well as scattered, large naevi upon the rest of the body. The nipples were widely spaced, and the breasts very minimally developed. The facial appearance was very masculine, with hair on the chin and upper lip areas. Also evident was the abnormal structure of the vulva. Neither the large nor small labia were completely developed.

Examination of the internal organs revealed the following pathological findings. The coronary arteries were arteriosclerotic. Both lungs showed lower lobe bronchopneumonia as well as terminal edema. The liver was small, yellowish-brown and congested. A lack of recognizable lymphatic structures in the small intestine was observed. The «tumor of the right lung» seen previously in x-rays was found to arise from the right vagal nerve and was entirely separate from the lung, although it did compress the upper lobe. It was about the size of a fist and lay substernally in the right upper thorax aperture. It was found to be directly connected to another tumorous growth attached to the right common carotid artery. The thyroid gland lay next to but was not connected to this tumor. It was somewhat enlarged and on its cut surface revealed multiple colloid adenomas. The trachea was quite short (10 cm. from the vocal cords to the bifurcation). The para-tracheal, bifurcation and hilus lymph nodes were all small.

The organs of the urogenital tract deserve special attention. The external and internal genital organs as well as the abdominal aorta, the kidneys and the adrenals were dissected out together.

The kidneys and adrenals were of normal structure. Both ureters opened properly into the rather large bladder. The uterus was extremely small, corresponding to that of a 4-5 year old child. It measured 40 mm.

in length, its isthmus was 10 mm. wide, and its corpus was 30 mm. across from one tube angle to the other. Fallopian tubes could be distinguished on both sides. However, the ovaries appeared to be lacking, with only rudimentary gray-white streaks in their place. On the right side was a white streak 40 mm. in length and 5 mm. wide at its center. Upon cutting this structure, a stroma-poor tissue, heavily vascularized, was observed. The right Fallopian tube was long (11 cm.) and narrow. Its fimbriated end was hypoplastic. The left ovarian streak is also long and narrow, measuring 30 by 5 mm. It is attached by a mesenterium which would correspond to a mesovarium. The vagina is extremely small, allowing only the little finger to pass.

Examination of the brain showed it to be large, symmetrical and of a solid consistency. The basal arteries were somewhat coiled, but did not exhibit signs of arteriosclerotic change. The cut surface revealed congestion, and many pinpoint areas of bleeding were present, especially in the medullary region of the occipital lobe. The cortex was thinner than normal. The ventricles were slightly enlarged.

HISTOLOGY

Liver: the parenchyma shows diffuse fatty infiltration mostly of fine fat droplets. Evidence of congestion was also present. The Glisson's capsule was enlarged and infiltrated with lymphocytes in many places.

Myocardium: fatty change was also evident here. Small groups of leucocytes were scattered throughout the field examined.

Pancreas: few Langerhan's islands are present. Those present are fatty and degenerated. One place shows a large node which resembles thyroid tissue, since follicular structures are present containing colloid substance. The vessels of the gland are heavily sclerotic.

Breast: is almost entirely fibrotic. Mostly scar tissue and a few excretory ducts are visible. On the whole the picture resembles that of a gynecomastia. Actual glandular tissue is absent.

Hypophysis: the adenohypophysis shows an extensive fibrosis as well as a small adenoma arising from the chromophobe cells. The junction between the neuro and adenohypophysis is indefinite, and the small neurohypophysis itself contains some pigment cells as well as layers of basophilic cells near the pars intermedia.

Lung: reveals passive congestion and small areas of atelectasis. Patchy areas of bronchopneumonia are also present.

Tumor in right common carotid artery area: is a fibroneurinoma containing spindle-like cells forming bundles which partly interweave. Areas of hyaline degeneration are pronounced, and in many places bleeding into the tumor has occurred. Cystic degeneration is also evident, these areas containing increased vascularization and deposits of hemosiderin pigment. Other parts of the tumor reveal a more primitive structure.

Brain: the cerebral cortex, the medullary substance and the basal ganglia all show extensive passive hyperemia. The intracerebral vessels exhibit hyalinization of the vessel walls. The perivascular lymph spaces, Virchow-Robin spaces, are enlarged. Multiple small infarcts are distributed throughout the brain, however, there is no cyst formation nor actual liquefaction of these areas.

Ovary: systematic investigation of the ovary was carried out using 10 different sections (blocks) of the entire gonadal streak. The slides revealed that parts of the epoophoron are present. There are ducts evident which are lined by cuboidal epithelium. Otherwise, there is extremely little evidence of *ovarial-like* tissue. That which is present is partly made up of a fibrous dense stroma which corresponds to normal ovarian supporting tissue. There are no ovarian follicles present, nor any fibrous scars or signs of follicle atresia. However, the rete ovarii is well developed. There are also adenoma-like structures present in the rete, some of which are considerably widely spread out. The surface of these fibrous, ovarian-like remnants exhibit some small cysts.

Uterus: the endometrium shows a lack of glandular structures. Here also one finds mostly a fibrous supporting tissue surrounding a few separate glandular tubes. The epithelium of these glands is flat.

DISCUSSION

The term gonadal dysgenesis refers to that state in which germ cells are lacking in female developed internal and external genital organs. The rudimentary gonads usually contain remnants of the normal structure such as an ovarian stroma or a rete formation. The chromosomal sex in this syndrome can be XX, XO or XY, and newer findings reveal that various mosaics of these chromosome patterns also exist.

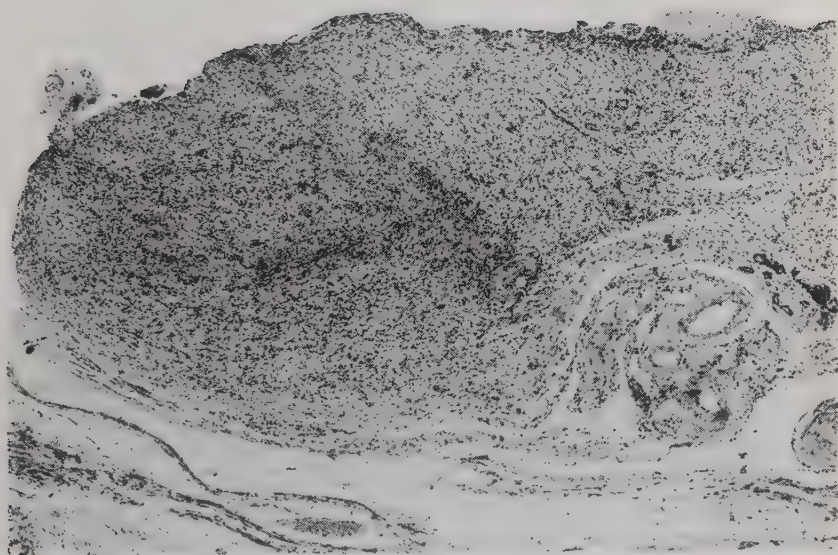


Fig. 1

Cross section of gonadal ridge showing cortex and mesonephric elements of Medulla. (H. E., 40 x)



Fig. 2

Details of the gonadal cortical stroma. (H. E., 280 x)

Since the primitive gonad is bipotential, its final state as either an ovary or a testis depends upon the dominant sex-determining genes on the X and Y chromosomes. Y chromosomes contain genes that influence development of the medullary or mesonephric portion of the primitive gonad which forms the testis. X chromosomes contain genes that lead to development of the thickened coelomic epithelium comprising the cortex of the primitive gonad; this forms the ovary. If abnormal chromosome patterns occur, as for example in the XXY pattern of Klinefelter's syndrome or the XO of Turner's syndrome, then various disturbances in the differentiation of the genital organs result. The XXY individual develops hypoplastic testes apparently due to the male-determining genes of the Y chromosome. The XO individual develops only rudimentary gonads, which infers that two X chromosomes are necessary for complete ovarian development.

The XO chromosomal aneuploidy results in a phenotypic expression that can be clinically recognized at all ages. Nuclear sexing of such individuals by determining the presence or absence of a Feulgen-positive nuclear appendage (sex chromatin) in tissue cells (Barr, 1949), in over 80 % reveals a lack of the chromatin substance. Since sex chromatin is normally only present when the XX chromosome complement exists, its absence can be taken to mean that one of the X chromosomes is missing, e. g. XO syndrome, or that it has been replaced as in the normal XY constituent of the male. The usual frequency of "sex chromatin-positive" cells taken by a buccal smear in XO individuals is 0-4 % at the most. Individuals having mosaic chromosomal structures usually have more than 4 % chromatin positive cells by buccal smear. Thus, chromatin negative findings, as in the presented case of 0 % (two different laboratory determinations), is strong evidence that the XO pattern is present.

Lennox advances the following hypothesis to explain the relationship of the sex chromatin to X chromosomes. He believes that all X chromosomes are potentially able to produce sex chromatin bodies. However, each separate autosomal complement contains a suppressing factor which prevents one X chromosome from developing its chromatin body. Therefore, the number of positive sex chromatin cells in a buccal smear, for example, would represent the number of X chromosomes present minus the number of autosome sets. Thus, one would simply add one to the number of sex chromatin bodies to arrive at the number of X chromosomes. Since there were no "Barr bodies" found in the presented case, zero plus one would result in the designation of an XO chromosomal complement. Lennox came to his conclusions from evaluations of the works of Ohno et al. who made tissue culture studies on the rat and on man. They found that only one chromosome revealed a definite hetero-

pyknosis during prophase in the normal female; none did in the male. This one chromosome was identified as an X chromosome, and its change in appearance was attributed to the building of sex chromatin.

The absence of drumsticks in peripheral blood smears also points to the XO pattern in this case. De La Chapelle concluded, in his extensive survey of 24 patients with gonadal dysgenesis, that oral mucosa smears are of great value in detecting XO cases. However, he found that the detection of mosaicism by this method was extremely difficult because the sex chromatin findings resemble so closely those found in normal females. None of his XO cases were found to have drumsticks in their neutrophil polymorphonuclear leukocytes. Unfortunately, the lack of an idiogram in the presented case makes it impossible to rule out definitely a possible mosaicism.

Further evidence indicating that this case belongs in the Turner or XO Syndrome group can be found in evaluating the phenotypic expression. Lemli and Smith studied the differentiated phenotype in 25 patients aged one month to 20 years. They listed 25 possible "potential anomalies" and concluded that no individual possessed less than six of these traits. The frequency and type of various anomalies compared to the findings in the presented case can be seen in the following table:

Anomaly	%	Presented Case
Short stature	100	+++
Broad chest and wide spacing of nipples	92	+++
Swelling of dorsal finger surfaces	92	?
Low posterior hairline	88	++
Prominent ears	84	+
Small highly arched palate	84	—
Small mandible	80	—
History of congenital lymphedema	80	?
Abnormal fingernails	80	+
Cubitus valgus	72	+
Short neck	68	+++
Unusual facies	64	+++
Increased number of pigmented naevi	64	++
Renal anomalies	64	—
Webbed neck	52	—
Swelling of toe surfaces	48	—
Clinodactylia	48	?
Moderate pectus excavatum	44	—
Persistence of epicanthal folds	44	—
Inverted nipples	36	—
Short 5th. fingers	36	—

Coarctation of aorta	36	—
Eyelid ptosis	20	—
Mean distal axial triradius over 35 %	20	?
Other cardiovascular anomalies	16	—

As can be seen, six definite characteristics as well as three additional, less striking traits are distinguishable in this case. Another prominent finding not taken into account by Lemli and Smith is the extremely hypoplastic external genitalia found here. Most of their case studies were of children where this secondary sexual characteristic naturally was not obvious. Also another sexual characteristic, the development of pubic hair, is only sparsely present. The axillary hair is practically non-existent, while the pubic hair is scanty. The fact that any pubic hair grows at all can be explained by the role of the adrenal gland which apparently has more to do with hair development than the gonads. Finally, the undeveloped breasts also add to the typical phenotypic expression of a Turner's syndrome.

The extreme degree of osteoporosis which led to the patient's incomplete recovery from her fracture is also a frequent sequel of Turner's syndrome. Usually the manifestations of osteoporosis are at a much earlier age due to the lack of estrogens. Elliot et al. described a similar case of a fracture of the neck of the femur in a twenty-one year old patient.

The hormone studies on this case are inconclusive. The usually increased elimination of gonadotropins in the urin, confirmed by many investigations, is not to be found here. However, normal values have also been repeatedly observed in classical cases of gonadal dysgenesis (Polani, 1961). The increased titer of phenol steroids (estrone, estriol, estradiol) can be explained by production of these hormones in the adrenal cortex. This interpretation would also serve to explain the presence of pregnandiol in the urin which certainly could not come from the dense connective tissue remnants representing ovaries. Hauser and Keller also noted slight quantities of pregnandiol in some of their cases. Unfortunately, no assay of 17-ketosteroids was performed. However, adrenal cortical activity was tested by injection of ACTH (Thorn test). The resultant drop in circulating eosinophils as well as the normal eosinophil count indicate that the titer of 17-ketosteroids was in all likelihood not significantly increased. The possibility that this titer was decreased cannot be ruled out, and perhaps the profound effect of the corticotropin (97 % decrease of eosinophils) does point to a low level, since the usual response to ACTH is a 70 to 85 % drop. Observations by Batrinos et al. indicate that the adrenal secretory capacity in most cases of gonadal dysgenesis is normal.

ACTH stimulation produced a normal response in eight patients — increased excretion of 17-hydroxycorticosteroids and somewhat less marked rise in the output of 17-ketosteroids.

The histological findings of the gonads represent basically the same observations of many investigators. Meyer in 1925 described essentially similar findings of a well-developed rete ovarii. Rössle and Wallert in 1930 also described the presence of the vestigial tubules of the epoophoron, lined by a low cuboidal or columnar, sometimes ciliated epithelium. The extremely small remnant of connective tissue, resembling ovarian supporting tissue, is the only structure found which represents an ovarian cortex. The possibility that this patient would normally have not had any follicles due to her postmenopausal age can be refuted by the total absence of fibrous scars from atretic follicles or any evidence of a corpus albicans. The adenoma-like structures seen in the rete are most likely of mesonephric origin and could correspond to the cystic and convoluted mesonephric tubules described by Epps et al. In contrast to other findings in cases of gonadal dysgenesis (Mayer, Epps, Hauser, Gloor et al.), no large, clear «hilar cells» or «Leydig cells» were visualized. Thus, in review of the microscopical evidence, only medullary elements of the gonad arising from the mesonephron are present here. This is characteristically the case in Turner's syndrome.

Certain similarities of this case to a possible hypopituitary dwarfism warrants a discussion of differentiating the two. The major difference usually found is the high gonadotropin titer in gonadal dysgenesis. A low titer would definitely speak for hypopituitarism. The normal values present in this case are of no help in this instance. However, the negative chromatin substance finding rules out a «female» chromosome complement which should exist if the patient actually were only suffering from hypopituitarism. Furthermore, the ovaries of a non-gonadal dysgenesis patient would certainly contain follicles in various stages of development and atresia leaving telltale fibrous scars. Pituitary dwarfs exhibit no pubic hair; this is only reduced in cases of dysgenesis. The various stigmata of Turner's syndrome, e. g. short neck, wide chest, cubitus valgus etc., are naturally not found in pituitary dwarfs.

S U M M A R Y

A case of a sixty-four year old female phenotype with signs of Turner's syndrome is described and evaluated with the aid of autopsy findings. The genetic and physical characteristics of gonadal dysgenesis are discussed and a differential diagnosis pertaining to this case presented.

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